REMARKS

Reconsideration is respectfully requested in view of the above amendments and the following remarks. Claims 20-30 are cancelled. Independent claims 1, 2, 14, 19, 35 and 39 have been amended to clarify that the digestion products do not need to be purified before the ligation reaction. Independent claim 14 in its currently amended form requires the presence of an unpurified mixture of digestion products and the DNA ligase. The support for the amendments is found at least in paragraph 0223 of the application as published (US20050227316) and in original claims 19 and 20. Dependent claim 19 has also been amended. The support for the amendments is found at least in Fig. 20 of the application. Accordingly, the amendments do not introduce any new matter.

The instant invention is drawn, in one aspect, to a method for ligation of a plurality of DNA segments to obtain a ligation product that comprises sequences from each of said DNA segments in a predetermined order, said method comprising: a) providing at least three DNA molecules, each comprising a DNA segment and a vector segment, wherein each DNA segment is adjacent to one or two other DNA segments in the ligation product, wherein each DNA segment comprises a first region having sequence identity with a first adjacent DNA segment and a second region having sequence identity with a second adjacent DNA segment, if present, and wherein each vector segment comprises a selectable marker and/or a counter-selectable marker; b) cleaving each DNA vector to produce a DNA segment with one or two ligatable ends, each said ligatable end comprising at least a portion of the region having sequence identity with an adjacent DNA segment; wherein at least one segment comprises two such ligatable ends after cleavage and wherein at least two DNA segments comprise exactly one such ligatable end, c) simultaneously ligating each DNA segment to the adjacent DNA segment or segments, wherein the DNA segment with one or two ligatable ends is not purified prior to said ligating; and d) selecting a ligation product comprising sequences from each of said DNA segments in a predetermined order, wherein said selection is based on the presence in a vector comprising the ligation product of a selectable marker and counter selectable marker of at least one of said three DNA vectors.

Rejection based on 35 USC § 102(b)

The Examiner rejected claim 1 as allegedly anticipated by Hodgson (US 20020025561). Applicants respectfully traverse.

Claim 1 has been amended to further underscore an important advantage of the instant invention. Namely, the products of the enzymatic digestion reaction do not need to be purified before ligation. Further, claim 1 has been amended to require the presence of a counter selectable marker. Hodgson does not disclose these limitations, either explicitly or by inherency.

Since a reference anticipates a claim only if it discloses all limitation of that claim (see, e.g., MPEP § 2131), and since Hodgson does not disclose at least two limitations of claim 1, the instant rejection ground is improper. Accordingly, Applicants respectfully request the Examiner to withdraw rejection of claim 1 as anticipated by Hodgson.

Rejection based on 35 USC § 103

The Examiner rejected claims 1-20 and 31-39 as obvious over Hodgson in combinations with Slater (US20050074883), Santi (US 20040166567) and Gokhane (*Science*, 1999, 284:482-485). Applicants respectfully traverse.

Before engaging in the argument on the merits of the rejection, Applicants wish to address the propriety of using Slater and Santi for rejection of the instant application.

Regarding Slater, Applicants respectfully note that it was published on April 7, 2005, which is after the filing date of the instant application, which is April 7, 2004. Accordingly, Applicants assume that Slater is a Section 102(e)/103(a) reference. This reference can be overcome if the Applicants show that the date of the invention precedes the filing date of Slater, which is October 3, 2003. Slater does not refer to any earlier application. See MPEP § 2136.05 stating, in relevant part, that

> When a prior U.S. patent, ** U.S. patent application publication, or international application publication* is not a statutory bar, a 35 U.S.C. 102(e) rejection can be overcome by antedating the filing date (see MPEP § 2136.03 regarding critical reference date of 35 U.S.C. 102(e) prior art) of the reference by submitting an affidavit or declaration under 37 CFR 1.131 or by submitting an affidavit or declaration under 37 CFR 1.132 establishing that the relevant disclosure is applicant's own work.

Applicants respectfully submit a Declaration of Dr. Sarah J. Reisinger, establishing that the date of the invention of the instant application precedes the filing day of Slater.

With regard to Santi, Applicants respectfully note that Santi was published on August 26, 2004, which is after the filing date of the instant application. Accordingly, Santi is also a § 102(e)/103(a) reference. Applicants further respectfully note that Santi and the instant application were subject to assignment to the same entity, namely, Kosan Biosciences. Applicants bring the Examiner's attention to 35 USC § 103(c) which states, in relevant part, that

> (1) Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Accordingly, under § 103(c) Santi is disqualified as a proper prior art reference for this rejection ground.

For these reasons, the only references cited by the Examiner which can properly be used for the § 103 rejection are Hodgson and Gokhane. For the purpose of efficiency, Applicants will address the disclosure of Gokhane first.

Gokhane only discloses recombination of structural modules from the naturally occurring PKSs. See Office Action at page 6. Gokhane does not cure the deficiencies of Hodgson. Unlike Applicants presently amended claims neither Hodgson nor Gokhane require the presence of a counter selectable marker and the absence of nucleic acid purification of the products of enzymatic digestion. Furthermore, Gokhane does not disclose or suggest directional cloning of multiple synthons at the same time, as claimed by the Applicants. Notably, the independent claims of the instant application, namely, claims 1, 2, 14, and 35, do not recite any specific gene, let alone recombinant PKSs. Accordingly, Gokhane is irrelevant to the analysis of obviousness of claims 1, 2, 14, and 35. Under MPEP § 2143.03, "[i]f an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious." Accordingly, if the independent claims of the instant application are not obvious, as will be shown below, Gokhane is irrelevant to the obviousness of the instant claims.

Considering the above, Hodgson is the only relevant reference to consider in this ground for rejection of the independent claims.

As discussed above, Hodgson does not disclose or suggest the additional limitations of the method claims, namely, that the fragments are ligated without an additional step of purification between the step of cleaving those fragments from vectors and the step of ligating these fragments. In fact, Hodgson explicitly states that "the released insert fragments are isolated and purified from the vector fragments." See Hodgson, paragraph 0031, emphasis added. Also see Hodgson, paragraph 0051 ("This [insert isolation and purification] can be done by any methods but is usually done by digesting clones with Sap 1, and by running the digested DNA on agarose gel... gel plugs containing the bands ... are removed from the gel and extracted using QIAquick gel extraction kits.")

In addition, Hodgson does not disclose or suggest the counter selective markers, and discloses that the colonies are selected using blue-white selection indicative of functional β-gal expression or absence thereof. This simplified clone selection method is most suitable, if not singularly suitable, for methods entailing the presence of only one vector. Notably, the blue-white selection method does not allow differentiation between the clones having the desired construct and the clones having a single insert ligated back into the vector it was excised from.

Since Hodgson purifies his fragments of interest, one of skill in the art would have figured out that counter selection markers are not needed in Hodgson's invention.

Applicants further direct the Examiner's attention to the Declaration of Dr. Reisinger. In the Declaration, Dr. Reisinger states that the use of two-marker vectors provided unexpected and clear advantage over one-marker vectors. Specifically, when the inventors used one-marker vectors, they found that 28% of the clones were false-positives. Such a high percentage of false positive clones necessitates additional steps of verification whether the selected clone is truly or falsely positive. In contrast, when two-marker vectors were used, no false positive clones were encountered. Accordingly, the use of two-marker vectors, as claimed by the applicants, makes the multiple-fragment cloning procedure even more efficient.

Thus, Hodgson teaches away from the subject matter of the independent claims 1, 2, and 35. Therefore, for these reasons, claims 1, 2, and 35 are non obvious. Claims 3-13, 31-34, and 36-39 depend on one of claims 1, 2, and 35. Since these independent claims are not obvious in view of Hodgson, the claims dependent from these independent claims are also not obvious.

Applicants respectfully note that one using Hodgson's system would have to either a) purify inserts from the respective reaction mixtures or b) re-analyze the clones of cells

transformed with the ligation products. Advantageously, neither of these steps needs to be performed using the methods of the instant invention. Considering that at least three (and likely more than three) vectors and corresponding inserts are present during the method of the instant invention, performing additional insert purification and/or clone analysis (e.g., restriction analysis) would take significant amount of time.

Regarding amended claim 14, the composition recited therein requires the presence of both DNA ligase and an unpurified endonuclease digestion product. As discussed above, Hodgson teaches away from using unpurified products of the digestion reaction. Accordingly, one following Hodgson would not consider adding ligase to the digestion mix before purifying the fragments of interest.

For these reasons, Hodgson does not disclose or suggest the subject matter of claim 14. Since claims 15-19 depend from claim 14, Hodgson does not teach or suggest the subject matter of any one of claims 15-19.

Accordingly, for these reasons, claims 14-19 are not obvious in view of Hodgson, and Applicants respectfully request the Examiner to withdraw this ground for rejection.

CONCLUSION

In view of these amendments and remarks, Applicants believe that the claims of this application are in condition for allowance and an early notice to this effect is earnestly solicited. If the Examiner does not believe that such action can be taken at this time or if the Examiner feels that a telephone interview is necessary or desirable, Applicants welcome the Examiner to call the undersigned at 609-844-3020.

The USPTO is authorized to charge Deposit Account No. 50-1943 for any charges in connection with this matter.

Respectfully submitted,

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